

U.S. Application No. 09/603,663

**VERSION WITH MARKINGS TO SHOW CHANGES MADE**

**In the Claims:**

Claim 39 has been canceled.

Please amend claims 41 and 44 as follows:

41. (Amended) A method for selecting tester proteins capable of binding to a target peptide or protein and improving their binding affinity, comprising:

(a) causing mating between a first and a second population of haploid yeast cells of opposite mating types, wherein

the first population of haploid yeast cells comprises

a library of tester expression vectors for a library of tester fusion proteins having a diversity of at least  $1 \times 10^7$ , each tester expression vector comprising

a first transcription sequence encoding either the activation domain or the DNA binding domain of [the] a transcription activator, and

a tester protein sequence comprising a first nucleotide sequence encoding [the] a first polypeptide subunit, a second nucleotide sequence encoding [the] a second polypeptide subunit, and a linker sequence encoding a linker peptide that links the first and the second polypeptide subunits;

the second population of haploid yeast cells comprises a target expression vector comprising

a second transcription sequence encoding either the activation domain or the DNA binding domain of the transcription activator which is not expressed by the library of tester expression vectors, and

a target sequence encoding the target protein or peptide; and

either the first or second population of haploid yeast cells comprises a reporter construct comprising [the] a reporter gene whose expression is under transcriptional control of the transcription activator;

(b) expressing the tester fusion proteins from the library of tester expression vectors and the target fusion protein from the target expression vector;

(c) selecting those yeast clones in which the reporter gene is expressed, the expression of the reporter gene being activated by binding of the tester fusion protein to the target fusion protein;

(d) isolating the tester expression vector from the selected yeast clones; [and]

(f) mutagenizing the first and second nucleotide sequences in the isolated tester

expression vectors to form a library of mutagenized expression vectors;

(g) transforming the library of mutagenized expression vectors into the yeast cells of step (a).

(h) transforming the target expression vector of step (b) into the yeast cells simultaneously or sequentially with the library of mutagenized expression vectors;

(i) expressing the target fusion protein from the target expression vector; and

(j) selecting those yeast clones in which the reporter gene is expressed, the expression of the reporter gene being activated by binding of the tester fusion protein to the target fusion protein.

44. (Amended) A method for selecting single chain antibodies capable of binding to a human growth factor receptor, comprising:

(a) causing mating between a first and a second population of haploid yeast cells of opposite mating types,

the first population of haploid yeast cells comprising

a library of tester expression vectors for a library of tester fusion proteins having a diversity of at least  $1 \times 10^7$ , each tester expression vector comprising

a first transcription sequence encoding either the activation domain or the DNA binding domain of [the] a transcription activator, and

a tester protein sequence comprising a first nucleotide sequence encoding an antibody heavy chain variable region, a second nucleotide sequence encoding an antibody light chain variable region, and a linker sequence encoding a linker peptide that links the antibody heavy chain and light chain variable regions,

the second population of haploid yeast cells comprising a target expression vector comprising

a second transcription sequence encoding either the activation domain or the DNA binding domain of the transcription activator which is not expressed by the library of tester expression vectors, and

a target sequence encoding a human growth factor receptor; and

either the first or second population of haploid yeast cells comprises a reporter construct comprising [the] a reporter gene whose expression is under transcriptional control of the transcription activator;

(b) expressing the tester fusion proteins from the library of tester expression vectors and the target fusion protein from the target expression vector; and

(c) selecting those yeast clones in which the reporter gene is expressed, the expression of the reporter gene being activated by binding of the tester fusion protein to the target fusion protein.